Medical therapies and clinical trials

Judith Cave October 2023

Overview

- Review of current medical therapies*
- List of open clinical trials in UK currently

*only licenced and NICE approved therapies discussed today

Systemic options…

Somatostatin analogues

Peptide receptor radionucleotide therapy

Cytotoxic chemotherapy

Molecularly targeted therapies

The role of somatostatin analogues

Neuroendocrine tumours release unwanted hormones.

Somatostatin is an inhibitor of endocrine and exocrine hormone function in humans. Natural SST has a short half life, so synthetic versions have been made (octreotide, lanreotide, pasireotide), known as somatostatin analogues.

SST inhibits the secretion of growth hormone, prolactin, thyrotropin, cholecystokinin, gastric inhibitory peptide, gastrin, motilin, neurotensin, secretin, glucagon, insulin, and pancreatic polypeptide. Hence SSAs can help reduce symptoms of unwanted hormones.

Neuroendocrine tumours often express receptors for SST (known as SSTR2 and SSTR5). This means somatostatin analogues can also reduce tumour growth, by interacting with the somatostatin receptions.

The PROMID study

85 patients with metastatic or locally inoperable midgut Grade 1 NETs. Functioning and non functioning

Randomised either 30mg Somatostatin LAR or placebo

Outcome: Time to progression 14.3 months with Sandostatin LAR compared to 6 months with placebo

The CLARINET study

204 patients with metastatic or locally inoperable Grade 1 or 2 enteropancreatic NETs. Non functioning. Ki67 < 10%.

Randomised to either Somatuline Autogel 120mg or placebo

Results: Median time to progression not reached on Somatuline vs. 18 months on placebo. 65% of patients on Somatuline Autogel progression free at 24 months compared to 33% on placebo.

Systemic options…

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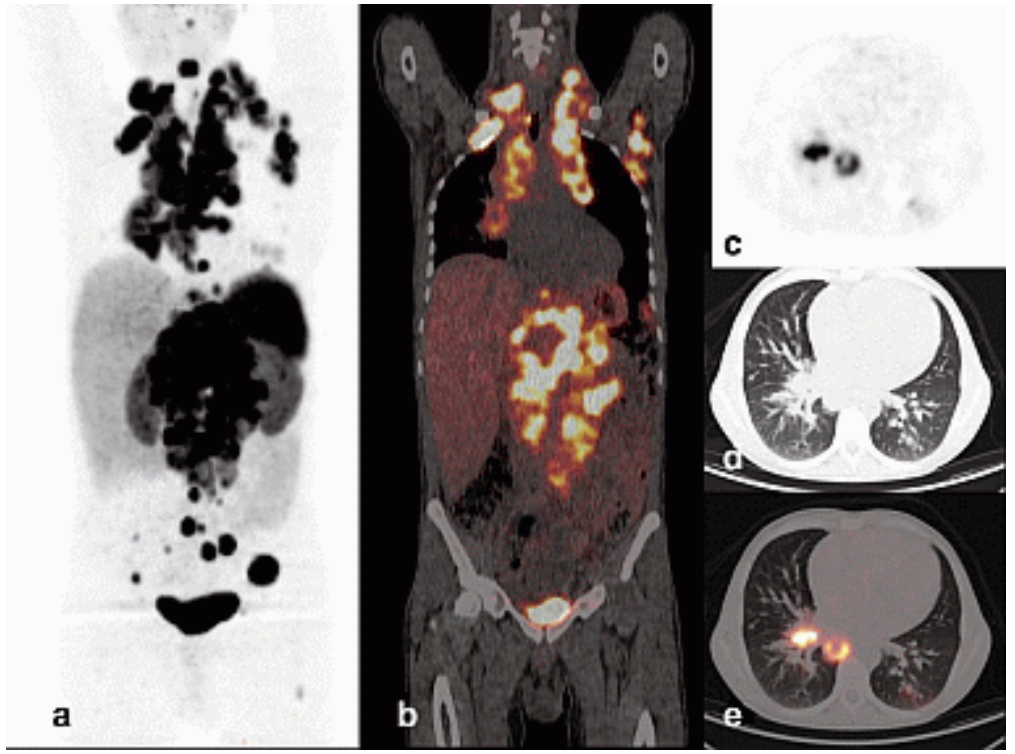
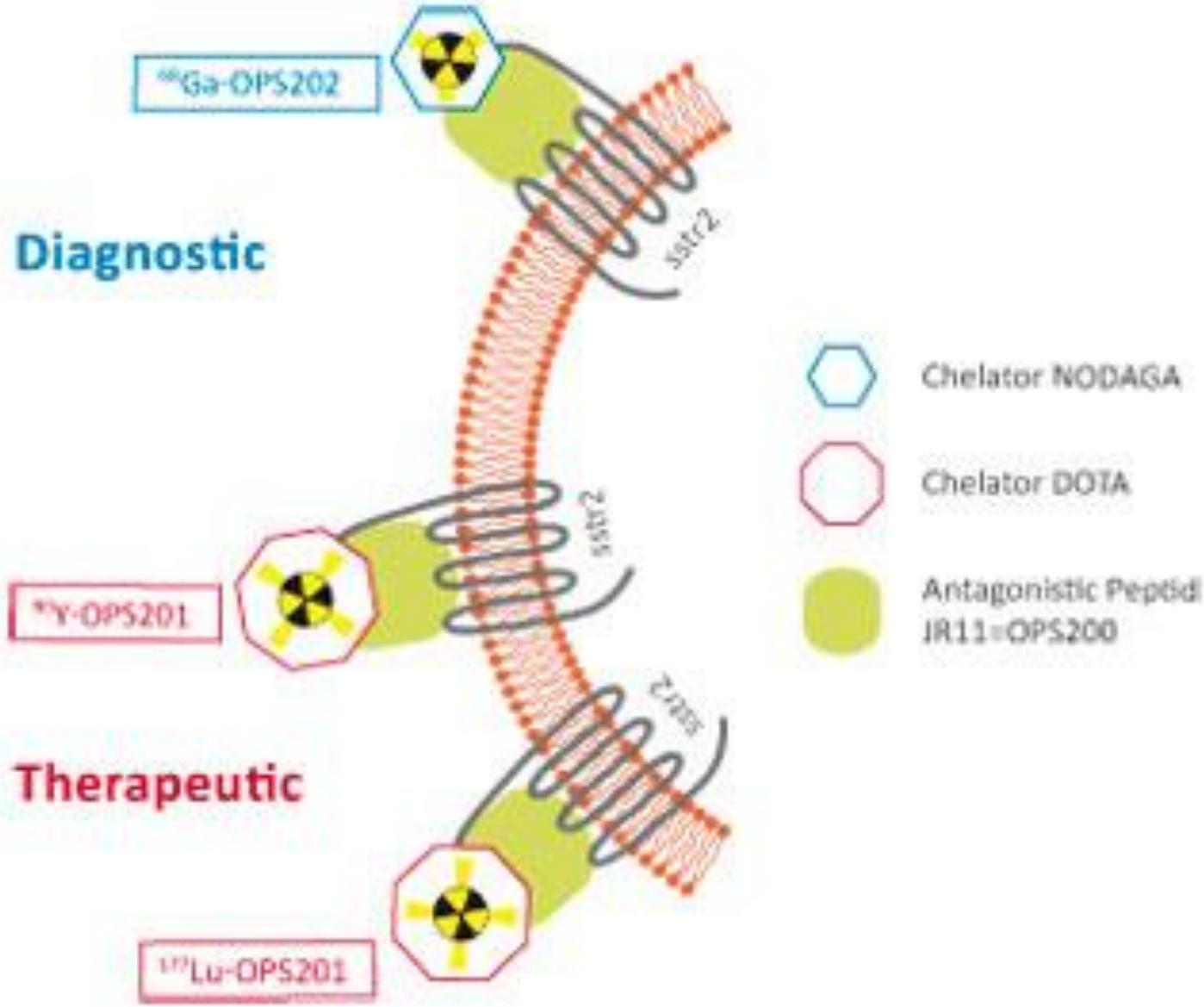
Cytotoxic chemotherapy

Molecularly targeted therapies

Peptide Receptor Radiotherapy

- Octreoscan to demonstrate Somatostatin Analogue uptake
- If sufficiently avid can deliver therapy
- Typically a course of 4 treatments given at 2 monthly intervals

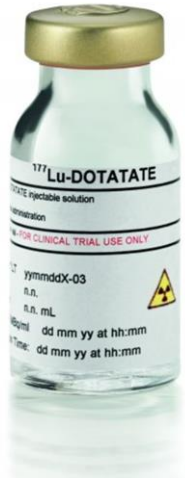



^{68}Ga-OPS202
Diagnostic
sstr2
^{90}Y-OPS201
sstr2
sstr2
Therapeutic
^{177}Lu-OPS201
Chelator NODAGA
Chelator DOTA
Antagonistic Peptid
JR11=OPS200

The role of PRRT

In patient with mid-gut NETS, lutetium 177 dotatate (lutathera/”PRRT”) plus octreotide has been proven to be superior to octreotide alone in terms of both survival and quality of life.

Your team can recommend PRRT if receptor status is positive, treatment would be safe, and they have access to funding.



Systemic options…

Somatostatin analogues

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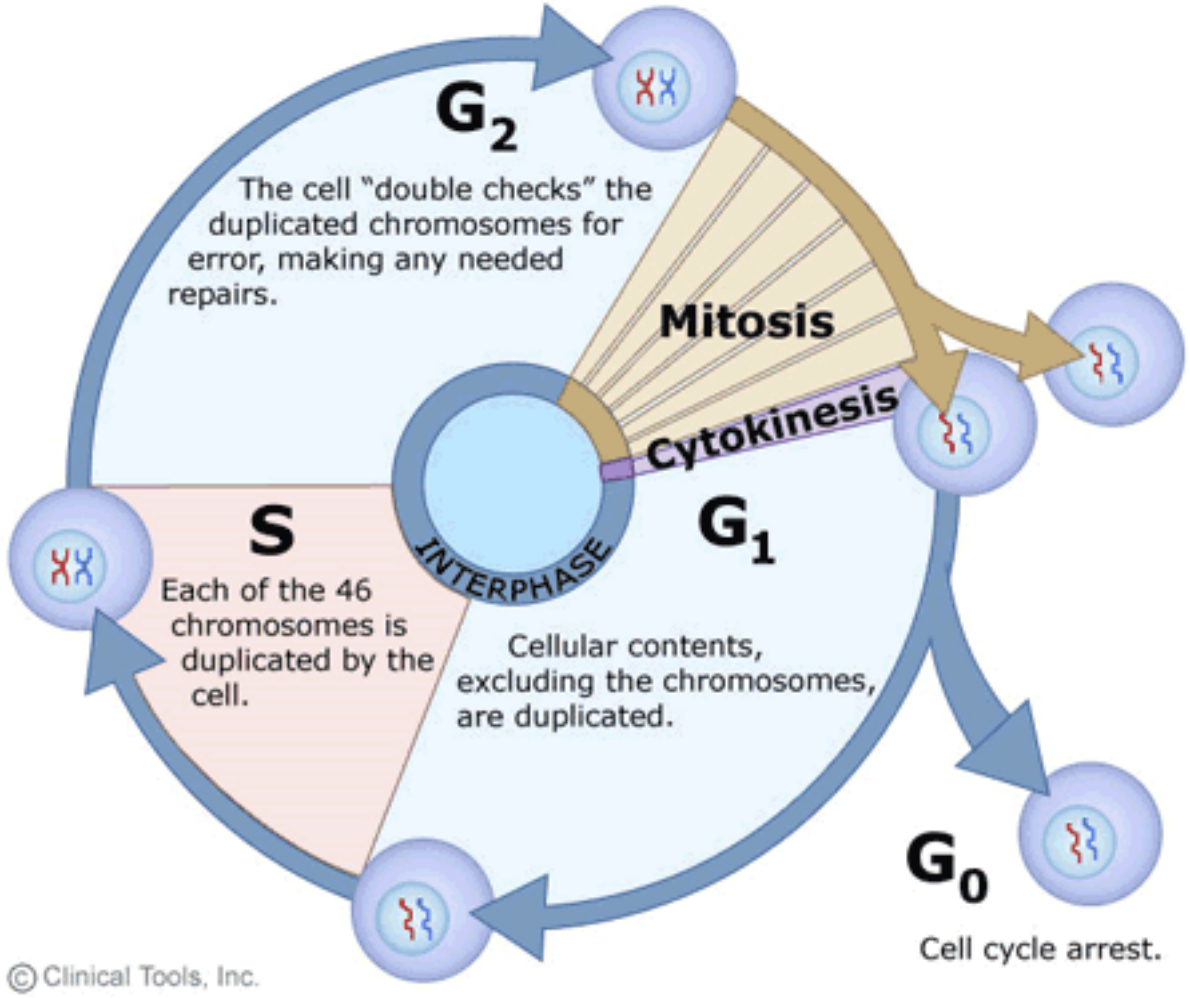
Cytotoxic chemotherapy

Molecularly targeted therapies

Cytotoxic chemotherapy

Cytotoxic chemotherapy = drugs which target cells as they divide and damage DNA leading to cell death

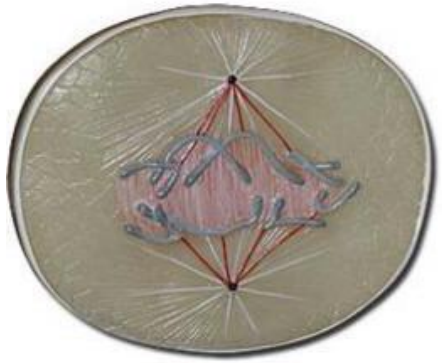


Interphase

Prophase

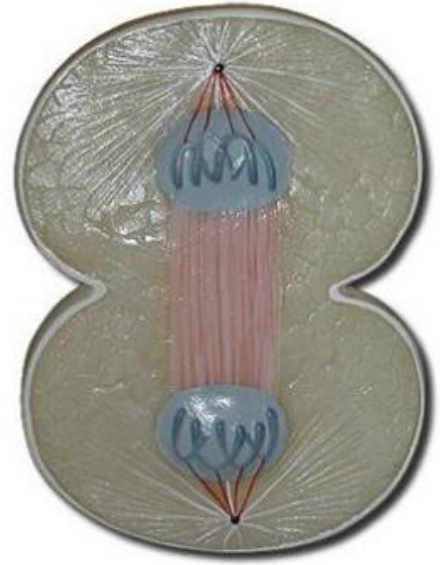
Prophase

Metaphase



Anaphase

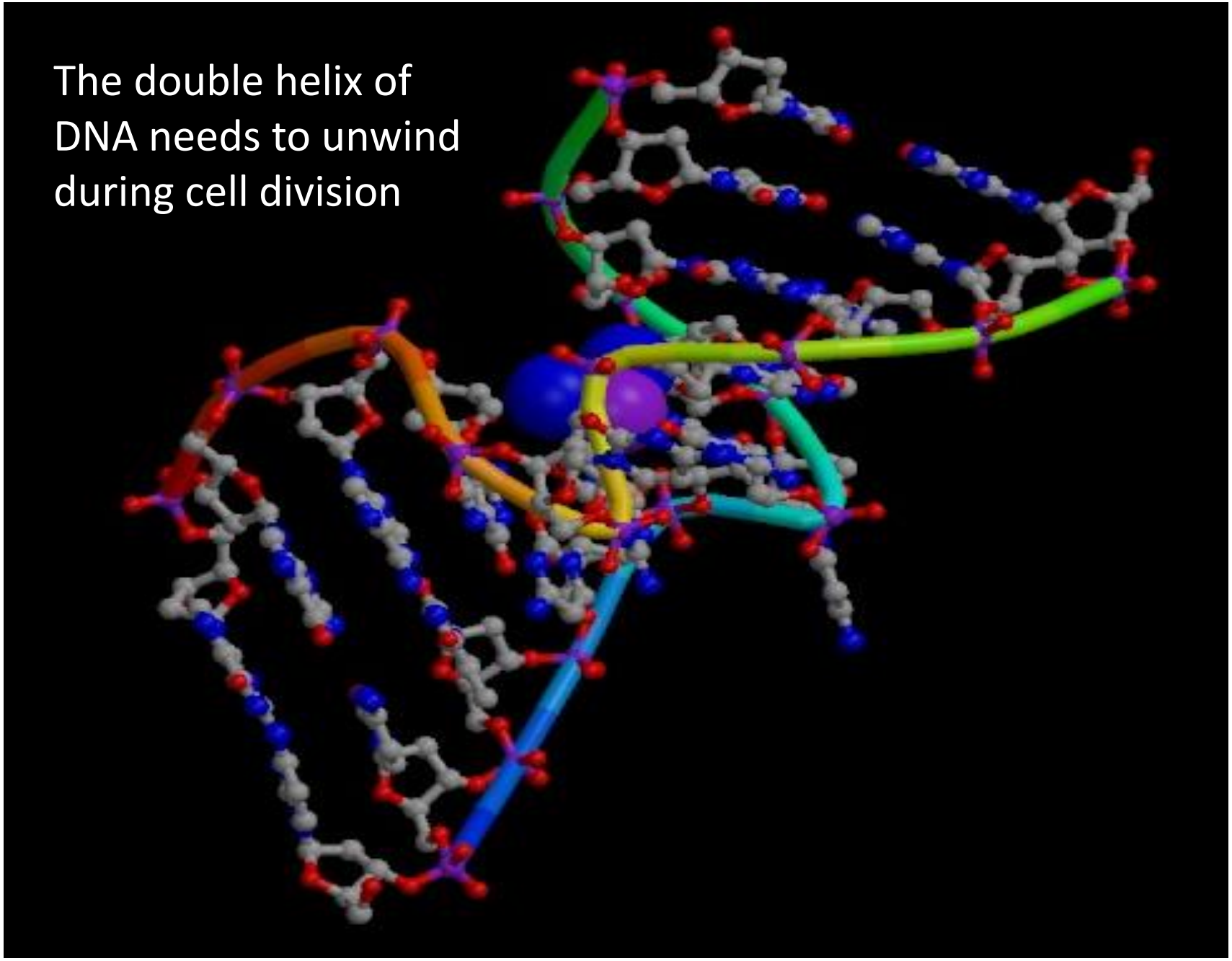
Anaphase



Telophase

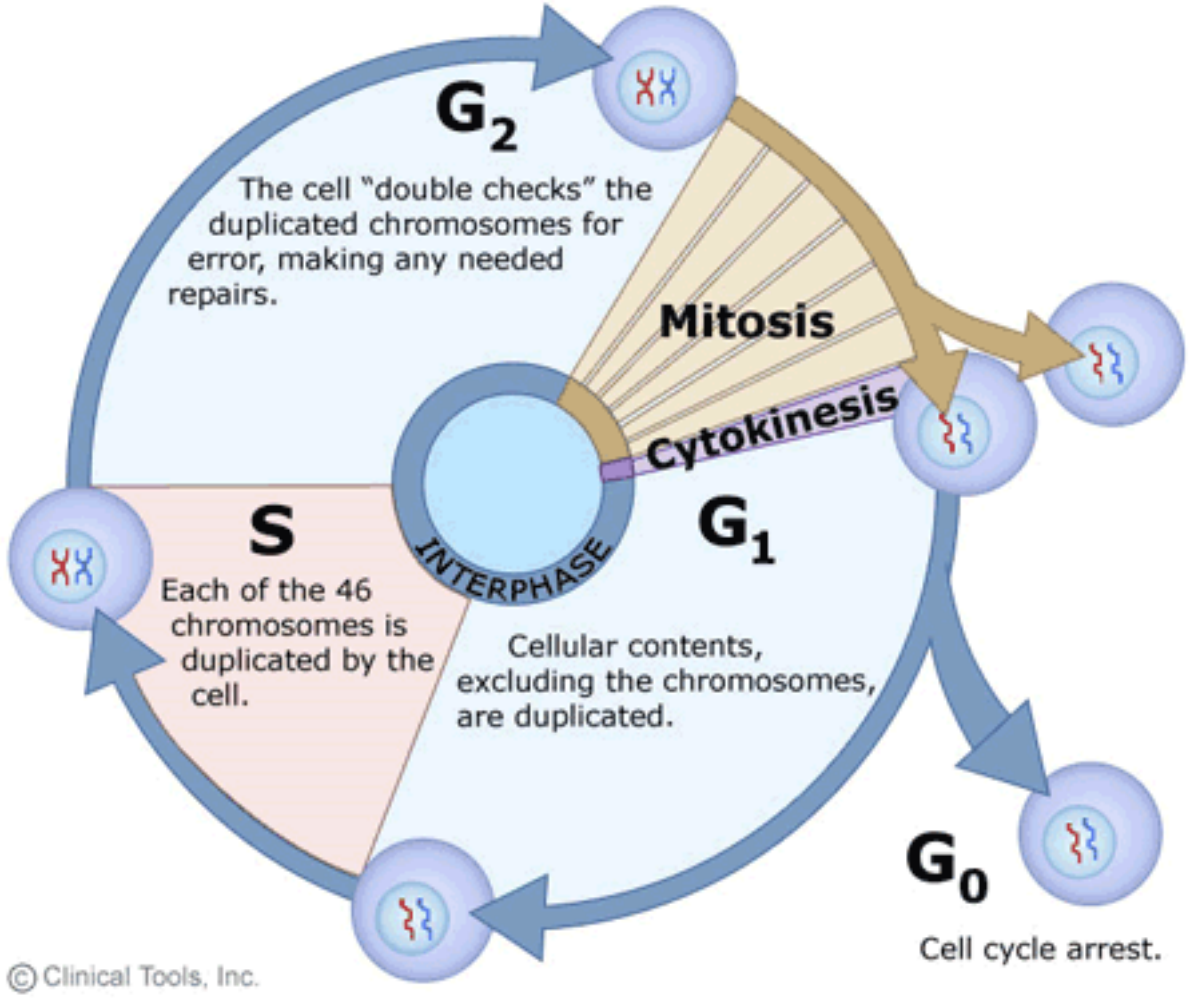
Interphase

The double helix of DNA needs to unwind during cell division

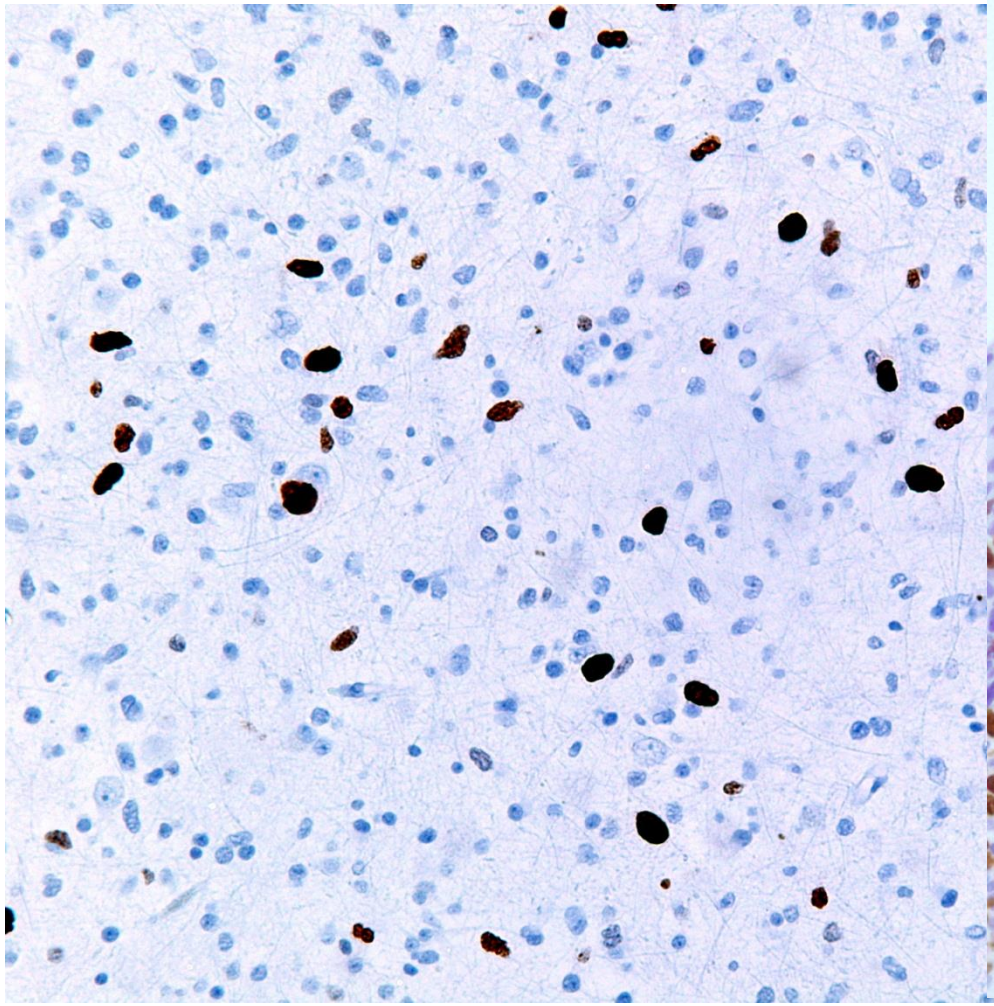


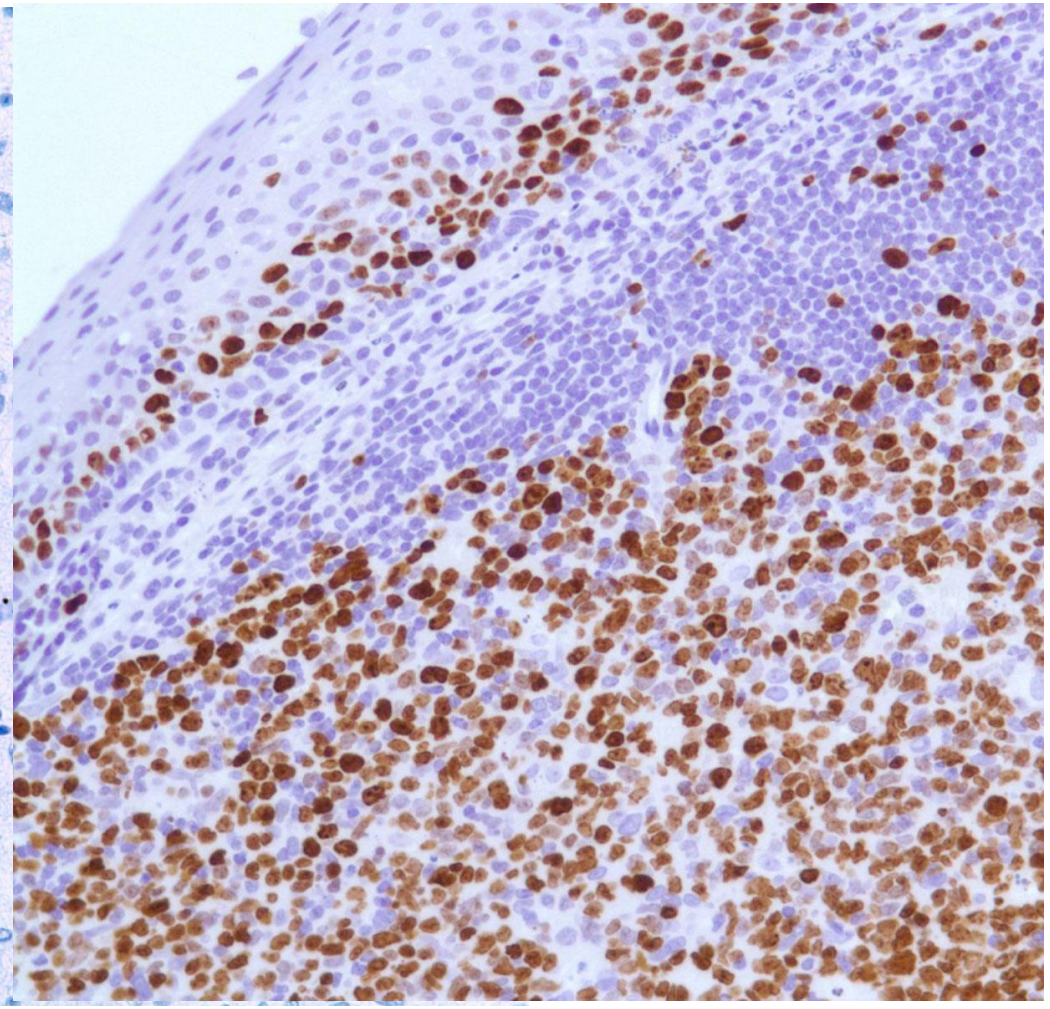
Cytotoxic chemotherapy

NB all chemo relies on cell division!



Dividing cells: a tumour-level view





Factors which might encourage the oncologist to recommend cytotoxic chemotherapy

- Disease not amenable to local treatment
- Patient is well enough that chemo would be safe
- High mitoses/Ki-67/grade
- Pancreatic primary

- … and patient choice

Systemic options…

Somatostatin analogues

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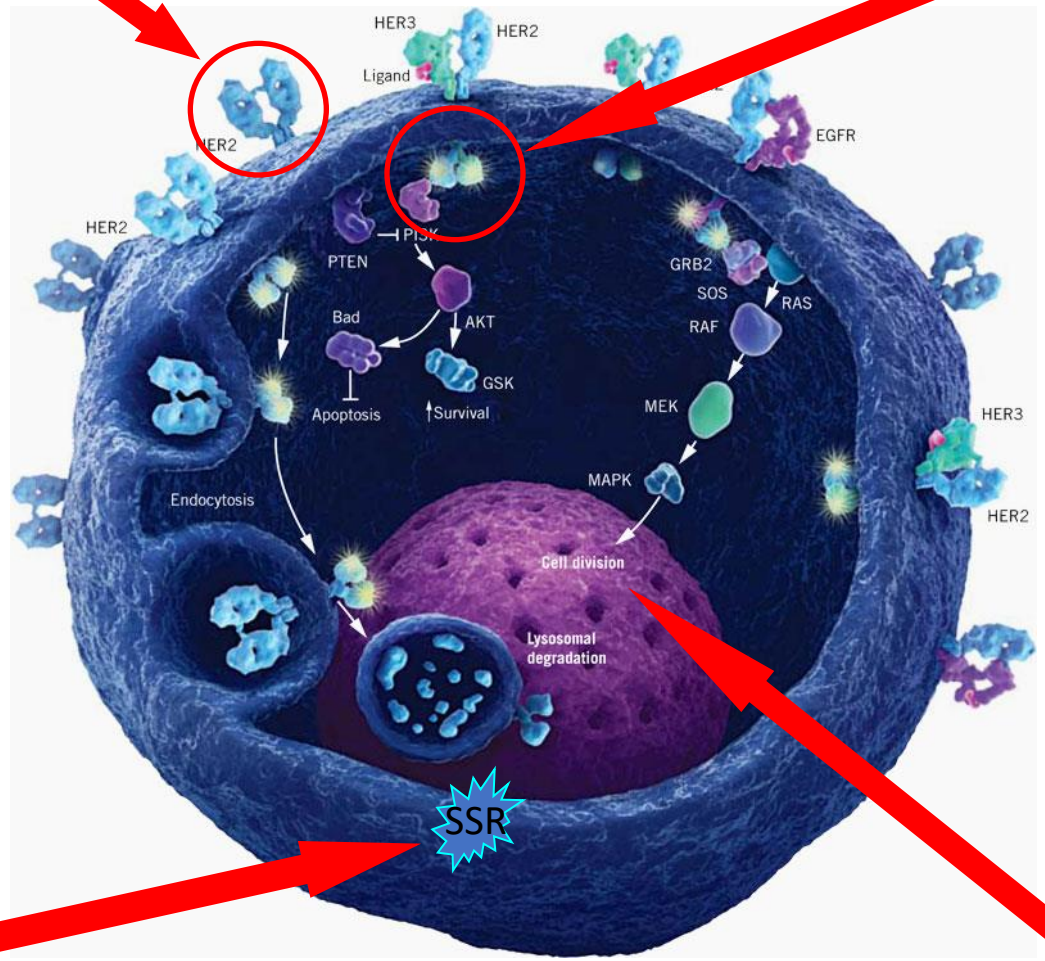
Cytotoxic chemotherapy

Molecularly targeted therapies

Monoclonal antibodies including immunotherapy

Small molecule targeted therapies;
E.g. Receptor tyrosine kinase inhibitors



Hormonal therapy

Cytotoxic chemotherapy

Molecular therapy – biological basis

The aim is to figure out what makes the NET cells different from the other cells, and target these differences.

It is known that:

- NETs are highly vascular tumours with increased VEGF expression.
- Genetic abnormalities in the mTOR pathway may be critical to the development of some NETs.

There are drugs which can target VEG-F and mTOR. So do they work?

Targeted therapies have activity

Primary site	Differentiation	Functional status	Targeted therapy options
Pancreas	Well differentiated	Not specified	Sunitinib*
Pancreas	Low/int grade	Not specified	Everolimus*
Lung/GI	Well differentiated	Non functional	Everolimus

*Choice of drug depends on medical history and patient choice. Can use both.

Advantages	Disadvantages
1. Tablets 2. Less side effects than chemotherapy 3. The idea sounds clever 4. Evidence that some patients achieve durable disease stability	1. Not available for all patients 2. Don't tend to shrink disease, just stabilise

Clinical trials currently open locally

Lantana	Patients entered into the study will receive ASTX727 orally up to 3 to 8 days prior to receiving Lutathera treatment to determine whether pre-treatment with ASTX727 results in re-expression of somatostatin receptor-2 in patients with metastatic neuroendocrine tumours.
Compose	The purpose of the study is to evaluate the efficacy, safety & patient-reported outcomes of peptide receptor radionuclide therapy (PRRT) with 177Lu-Edotreotide as 1st or 2nd line of treatment compared to best standard of care in patients with well-differentiated aggressive grade 2 and grade 3, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin.
Artisan	This is an open label study for patients with inoperable metastatic neuroendocrine liver deposits to see whether treatment with Selective Internal Radiation Therapy (TheraSpheres) could lead to improved treatment response rates with acceptable toxicity (minimal serious adverse events reported).

In summary:

Carcinoid syndrome and other functional symptoms require control, and SSAs are the mainstay of this treatment.

Other systemic options include PRRT, chemotherapy, and molecular therapies.

Clinical trials are investigating new types of PRRT and new ways of giving PRRT.